January 30, 2002

Lisa Navarro, Ph.D.
Manager, Toxicology Programs
CYTEC Industries Inc.
Five Garret Mountain Plaza
West Paterson, NJ 07424

Dear Dr. Navarro:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for 2-Amino-2,3-dimethylbutanenitrile, posted on the ChemRTK Web Site on September 18, 2001. I commend CYTEC Industries Inc. for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Chemical RTK HPV Challenge Program website EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the attached Comments on the Chemical RTK web site within the next few days. As noted in the comments, we ask that you advise the Agency, within 60 days of the posting on the Chemical RTK website, of any modifications to the submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit general questions about the HPV Challenge Program through the Chemical RTK web site comment button or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Attachment

cc: W. Sanders
A. Abramson
C. Auer
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
2-amino-2,3-dimethylbutanenitrile

SUMMARY OF EPA COMMENTS

The sponsor, Cytec Industries, Inc., submitted a test plan and robust summaries to EPA for 2-Amino-2,3-dimethylbutanenitrile (CAS #13893-53-3) dated July 20, 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on September 18, 2001.

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical and Environmental Fate Data. All appropriate SIDS-level tests/estimations have been performed and adequate robust summaries have been submitted.

2. Health Endpoints. EPA reserves judgement on whether 2-amino-2,3-dimethylbutanenitrile meets the criteria for a "closed system intermediate," pending the receipt of additional information. *In vitro* chromosomal aberration testing is needed because data are lacking for this endpoint. In addition, the submitter needs to provide a robust summary(ies) for the developmental data from the closest structural analog(s) to support the submitter's approach for this endpoint.

3. Ecotoxicity. All appropriate SIDS-level tests have been performed and adequate robust summaries have been submitted.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA COMMENTS ON 2-AMINO-2,3-DIMETHYLBUTANENITRILE
CHALLENGE SUBMISSION

Test Plan

Chemistry (melting point, boiling point, vapor pressure, water solubility, and partition coefficient).

Adequate existing data are available for these endpoints.

Environmental Fate (photodegradation, stability in water, biodegradation, and transport/distribution).

Adequate existing data are available for these endpoints.

Health Effects

The submitter proposes no additional health effects testing for 2-amino-2,3-dimethylbutanenitrile. The submitter notes that neither repeated dose toxicity nor reproductive toxicity data are needed because 2-amino-2,3-dimethylbutanenitrile is a "closed system intermediate" as defined by EPA for the HPV Challenge Program. In addition, the submitter states that chromosome aberration studies are not needed because positive results of this screen are only used to identify possible mammalian mutagens and carcinogens and the potential for exposure to this intermediate is limited to accidental release that

would likely be of "relatively short versus chronic duration" precluding the development of chronic disease such as cancer. And finally, the submitter suggests that developmental toxicity data are not needed because adequate analog data exist for several other aliphatic nitriles.

Reproductive and Repeat Dose Toxicity

The Guidance for Testing Closed System Intermediates for the Challenge Program http://www.epa.gov/chemrtk/guidocs.htm allows for a reduced testing proposal provided certain criteria are met. The information required to judge a "closed system intermediate" claim must address the following:

I. Site information.
    A. Number of sites.
    B. Basis for "closed process" conclusion at each site.
        1) Process description.
        2) Monitoring data showing no detection.
        3) In the absence of monitoring data, the basis for believing that releases do not occur.
    C. Data on "presence in distributed products."
II. Information on transport (mode, volume, controls, etc.)
III. A data search showing that the chemical is not present in other endproducts.

EPA believes that the submitter has generally addressed the criteria described above. However, EPA requests clarification on a number of points. The submitter indicates that manufacture employs a "closed process" utilizing a batch process, but there is no description of how the chemical is transferred through the various unit operations. Regarding transport, information on how the tank trucks are loaded and how they are unloaded at the use site (directly into reactor and/or storage vessels) is needed. Finally, a better description of the herbicide manufacturing process is needed to consider it "closed." Consequently, provided the submitter addresses the above points, repeated dose and reproductive toxicity tests do not need to be conducted (there is an adequate dermal repeat-dose study available).

Developmental Toxicity

The submitter needs to provide a robust summary(ies) for the developmental data from the closest structural analog(s) to strengthen the reasoning that the available data on analogs would produce similar adverse effects of embryolethality, fetotoxicity and teratogenicity in laboratory animals if 2-amino-2,3-dimethylbutanenitrile were to be tested.

Genetic Toxicity

Although adequate data exist on gene mutations, the submitter needs to conduct a test of the potential for 2-amino-2,3-dimethylbutanenitrile to produce chromosomal aberrations *in vitro*. The submitter's conclusion that the gene mutation test in bacteria is adequate to assess the potential for mutation cannot be supported because the mechanisms for producing gene mutations are different than those for producing chromosomal effects. The submitter also concludes that, because chromosomal aberration tests assess the possible carcinogenic potential of a chemical and the likely exposure to this material is not associated with chronic disease, the test is not needed. Chromosomal effects, however, can result from acute exposure and it is only the adverse effects that may take a substantial period of time to be expressed. Therefore, the submitter's conclusion that chromosomal aberration tests are not relevant is not well supported.

Ecological Effects (fish, daphnid, and algal toxicity).

Adequate existing data are available for these endpoints.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.